Great Lakes Air Center for Integrative Environmental Research (GLACIER)

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Director: Jack Harkema
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Center Overview:

Objectives: GLACIER is a multidisciplinary center with the objective to explore one of the most prevalent and important global health-environment interfaces: the inter-relationships between facets of the cardiometabolic syndrome (CMS) and air pollution. CMS is among the leading causes of death and threats to worldwide health. In tandem, exposure to air pollution, most notably fine particle matter ($PM_{2.5}$), remains highly prevalent and ranks among the leading causes of global mortality. Inter-relationships and health impacts of this burgeoning confluence between these two epidemics are of tremendous importance to elucidate. Our previous research has elucidated that $PM_{2.5}$ exposure plays a critical, yet under-appreciated, role in eliciting or exacerbating several key facets of the CMS-including elevating blood pressure, impairing vascular function, and even worsening metabolic insulin sensitivity and adiposity over a chronic duration. We have also found that the location of exposure, multipollutant context, and constituents within $PM_{2.5}$ affect the responses. The full extent and importance of inter-relationships between CMS and air pollution, individual susceptibility, specific pollution components, multipollutant atmospheres, $PM_{2.5}$ – ozone (O_3) coexposures, and underlying mechanisms of toxicity are all key issues remaining to be clarified. Our center's overall hypothesis is that $PM_{2.5}$ and O_3 are 1) capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on 2) the local multipollutant milieu, 3) an individual's pre-existing cardiovascular (CV) and metabolic condition (susceptibility), and 4) the interactive toxicity of $PM_{2.5}$ and O_3 coexposure.

Approach: In conjunction with 3 core facilities, GLACIER consists of 3 controlled exposure projects that each addresses specific aspects of the CMS-air pollution interface. The projects are scientifically integrated and interactive which will foster synergistic insights and cohesive synthesis of conclusions. *Project 1* aims to elucidate in humans the mechanisms of adverse CMS responses and the concentration-response relationships of acute exposures to differing $PM_{2.5}$ mixtures. *Project 2* aims to determine the short-term CV, autonomic and airway toxicity in rats exposed to differing $PM_{2.5}$ mixtures. *Project 3* expands upon the main theme by determining the CMS toxicity of differing longer-term exposures in mice. Each project will also investigate the role of pre-existing susceptibility and the comparative effects of $PM_{2.5}$ mixtures derived from 2-3 dissimilar multipollutant milieus of regional importance (near-roadway, industrial, transported). Toxic effects of $PM_{2.5}$, O_3, each alone and in combination, will be evaluated at each location.

Expected Results: We will address 1) temporal-response relationships to pollutant exposure and the development of CMS, 2) CMS effects of ozone and fine particle mixtures from 3 differing locations and their interactive toxicity, 3) the role of obesity and pre-existing cardiometabolic abnormalities in individual susceptibility, 4) concentration-response relationships for particles and O_3; and 5) mechanisms whereby air pollutants elicit CV and metabolic health effects. Our results will provide critical insights into the health effects of $PM_{2.5}$, O_3, and their coexposures in a multipollutant context.

Project 1: Cardiometabolic Effects of Exposure to Differing Mixtures and Concentrations of $PM_{2.5}$ in Obese and Lean Adults

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EPA Grant Number: R834797-01

Project Summary:

Objectives: We have discovered an important interaction between key aspects of the cardio-metabolic syndrome (CMS) and exposure to fine particulate matter ($PM_{2.5}$). Brief exposure to concentrated ambient $PM_{2.5}$ (CAP) for 2 hours triggers arterial narrowing (vasoconstriction), increased diastolic blood pressure (BP), and impairment of proper blood vessel function (vascular endothelial function (VEF)) 1 day after exposure – the latter occurring in a location-dependent manner suggesting that particle constituents are important determinants of these health effects caused by multipollutant exposures. Two pathways were implicated in these responses – 1) changes in autonomic nervous system (ANS) balance responsible for the increased BP and 2) systemic inflammatory responses for the slower impairment in VEF. Thought these findings help us understand how $PM_{2.5}$ might cause acute cardiovascular (CV) changes, several important issues remain to be clarified. Moreover, our previous studies also suggest that a more-encompassing, yet unappreciated, convergence might exist between $PM_{2.5}$ exposure and the CMS. Not only could obesity enhance the susceptibility to adverse health effects induced by $PM_{2.5}$ exposure, but $PM_{2.5}$ might promote the development of metabolic insulin resistance (IR), a central factor in the cause of obesity and the CMS itself. Our objectives are to investigate: 1) if exposure to CAP mixtures are capable of acutely instigating metabolic IR in addition to elevating diastolic BP and impairing VEF; 2) whether obesity confers enhanced susceptibility for these responses; 3) details of the mechanisms responsible for health effects; 4) the nature of the dose-response relationships even at concentrations below current 24-hour $PM_{2.5}$ standards; and 5) if CAP derived from 2 dissimilar multipollutant ambient $PM_{2.5}$ atmospheres cause differing CMS responses and the specific pollutants responsible.

Approach: We will achieve these aims by examining the BP and VEF responses, along with additional outcomes, in obese versus lean adults, caused by CAP exposures in 2 separate locals comprised of dissimilar $PM_{2.5}$ mixtures (industrial/urban versus a near-roadway/residential). The concentrations of CAP will be varied to include levels from below 35 to above 100 $\mu g/m^3$. Using state-of-the-art physiological testing and biomarkers, the mechanisms responsible for the alterations in CMS responses will be explored. The role of the ANS in the BP increase and the effectiveness of a prophylactic measure, $\alpha+\beta$ adrenergic blockade, in preventing this response will also be tested. Finally, we will evaluate whether exposure to CAP can acutely elicit metabolic IR.

Expected Results: This project will address questions with humans exposed to real-world $PM_{2.5}$, thereby providing findings of tremendous public health importance. The expected results will elucidate new insights into: the susceptibility of obese individuals to multipollutant atmospheric exposures, the extent of concentration-response relationships, the mixtures of $PM_{2.5}$ and their constituents responsible for health effects, and the mechanisms underlying the CV responses. Finally, we will explore the evidence for a novel $PM_{2.5}$ health effect – instigation of metabolic IR.

Project 2: Cardiometabolic, Autonomic, and Airway Toxicity of Acute Exposures to $PM_{2.5}$ from Multipollutant Atmospheres in the Great Lakes Region

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Co-PI: Greg Fink and James Wagner
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EPA Grant Number: R834797-01

Project Summary:

Objectives: Our objectives in Project 2 arise out of GLACIER's overarching hypothesis that the major air pollutants, fine particulate matter ($PM_{2.5}$) and ozone (O_3), are 1) capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on 2) the local multipollutant milieu, 3) an individual's pre-existing cardiovascular (CV) and metabolic condition (susceptibility factors), and 4) the interactive toxicity of $PM_{2.5}$ and O_3 co-exposure. Goals of Project 2 are to determine the cardiovascular (CV), autonomic nervous system (ANS), and airway toxicity in rats acutely exposed to concentrated ambient $PM_{2.5}$ (CAP) from distinct multipollutant atmospheres commonly found in the Great Lakes Region of the United States.

Approach: Our studies are extensions of our previous findings that CAP-induced alterations in heart rate variability are dependent on specific $PM_{2.5}$ emission sources in distinct locations in the Great Lakes Region. We will use a mobile air research facility (AirCARE 1) that is fully equipped with inhalation toxicology and atmospheric monitoring labs to conduct toxicology studies of rats exposed to CAP derived from real-world $PM_{2.5}$ in three distinct locations dominated by industrial/urban, transported/regional, or near-roadway/residential emission sources. Blood pressure, heart rate, heart rate variability and direct measurements of autonomic nerve activity will be continuously monitored during CAP and/or O_3 exposures in lean or obese rats with and without diet-induced facets of the cardiometabolic syndrome (CMS: hypertension, insulin resistance, endothelial dysfunction), respectively. Acute functional responses will be measured by radiotelemetry and will be correlated with specific PM constituents and their emission sources determined for the same highly resolved 30-minute timeframes, thereby making associations of exposure and health effects especially robust. Studies will feature novel real-time sympathetic nerve recordings during $PM_{2.5}$ and/or O_3 inhalation exposure. In addition, our project will highlight the unique integrative capabilities of our research team to link specific health cardiovascular effects in a sensitive obese population with PM content by a combined technological expertise that is unavailable elsewhere. Our GLACIER project will extend and complement the research of lean and obese human subjects (Project 1), conducted at the same exposure sites, by making invasive and prolonged measurements that could not be practically or ethically done in humans (e.g., repeated CAP exposures, continuous recordings of CV and autonomic nerve function, and microscopic examination of multiple organs for exposure-related pathology). Our acute animal studies will also overlap and integrate scientifically with the animal toxicology study of long-term air pollutant exposure in Project 3, where similar endpoints will be compared.

Expected Results: Our research has the potential to identify potentially harmful effects of exposures to specific $PM_{2.5}$ components, emission sources, and O_3 to cardiovascular function. It will also provide mechanistic evidence for the dysregulation of normal cardiovascular and metabolic pathways that leads to acute morbidity and mortality of obese individuals (susceptible population) exposed to $PM_{2.5}$ and/or O_3.

Project 3: Long Term Metabolic Consequences of Exposures to Multipollutant Atmospheres in the Great Lakes Region

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Co-PI: Qinghua Sun
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EPA Grant Number: R834797-01

Project Summary:

Objectives: We have recently demonstrated that short-term exposure to concentrated ambient particulate matter (CAP) elicits the development of hypertension and insulin resistance (IR) that are facets of the cardiometabolic syndrome (CMS) often associated with obesity and diabetes. We hypothesize that long-term exposure to CAP, along with expose to the common gaseous air pollutant, ozone (O3), interacts with host factors such as diet and genetic susceptibility, resulting in the development of CMS. Project 3 is an integral component of our Center's overarching theme that the major air pollutants, fine particulate matter (PM2.5) and O3, are 1) capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on 2) the local multipollutant milieu, 3) an individual's pre-existing cardiovascular (CV) and metabolic condition, and 4) the interactive toxicity of PM2.5 and O3 coexposure.

Approach: Our proposed experiments are natural extensions of the human controlled exposure research outlined in Project 1 and the acute animal inhalation toxicology studies in Project 2. We will conduct long-term inhalation toxicology studies of obese and/or diabetic mice exposed to CAPs with or without O3. In Aim 1, simultaneous chronic exposure of mice to CAP from two locations in Columbus OH, representing near-roadway/residential or transported/regional multipollutant atmospheres, will be examined alone and in combination with a high fat chow diet (HFC). The impact of CAP on various biological measures of CMS (e.g., glucose/insulin homeostasis, adipokines, insulin signaling, inflammation in adipose tissue) along with an analysis of CAP concentrations and components associated with these induced health effects will be evaluated in HFC-fed mice and in mice with a genetic propensity for developing Type II diabetes (KKA/y). In Aim 2, we will investigate the effect of CAP and O3 coexposures on the temporal development of IR and inflammation in fat (adipose) and lung tissues of KKA/y mice. We will also assess dose-response relationships of CAP and O3 mixtures on IR and innate immune responses that are pivotal to the development of metabolic derangement characteristic of CMS. Based on data from Aims 1 and 2, we will design further experiments in Aim 3, which will help us to assess if and how CAP from multipollutant atmospheres may potentiate inflammatory cell (i.e., monocyte) activation and infiltration into various organs and tissues that may play important roles in mediating adverse systemic metabolic effects. We will contrast the results of health effect studies conducted at specified sites in Columbus, OH with those conducted in Dexter and Detroit, MI, to try to elucidate the components of these disparate multipollutant atmospheres that are most responsible for the enhancement of the CMS.

Expected Results: Using state-of-the-art mobile inhalation exposure systems available at our laboratory (OASIS 1 and 2) and at Michigan State University (AirCARE 1 and 2), along with novel and high-resolution exposure characterization methods of our collaborators at The University of Michigan (Project 3) offers an unprecedented opportunity to elucidate relevant biological mechanisms responsible for the effects of ambient $PM_{2.5}$ and O_3 exposures on the pathogenesis of IR and other facets of the CMS. Insights from our studies will provide important guidance on how to better protect public health and susceptibility populations, like those suffering from obesity and diabetes, from the harmful effects of environmental exposure to air pollutants in the Great Lakes Region and elsewhere.

CORE: Exposure Characterization

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EPA Grant Number: R834797-01

Project Summary:

Objectives: In coordination with and support of the GLACIER Research Projects, the Exposure Characterization Core (ECC) will provide measurements of multi-pollutant exposures for both human subject (Project 1) and animal toxicology (Project 2 and 3) studies. The overall objectives of the ECC are to 1) determine the mass, size, and chemical composition of pollutants for each exposure period, 2) determine the atmospheric emission sources responsible for the observed exposure concentrations, and 3) provide a detailed assessment of the differences in air pollution composition, sources, and chemistry between each of the exposure sites across each of the Projects.

Approach: The ECC is highly innovative in design by the use of ambient particle concentrators coupled with mobile toxicological laboratories to evaluate the acute health effects of multi-pollutant atmospheres dominated by different chemical components and emission sources. These mobile labs will be stationed in three communities in Michigan (Detroit, Dearborn, and Dexter) for short-term exposure studies conducted in Projects 1 and 2, as well as two locations in Columbus, OH, for longer-term exposure studies in Project 3. The ECC will specifically utilize these exposure sites in Michigan and Ohio primarily impacted by (1) near-roadway motor vehicle emissions (two sites), (2) industrial point sources (one site), and (3) regionally transported air pollution (no local emission sources, two sites). Concurrent with the animal inhalation and human exposure studies, intensive characterization of the particles that are concentrated (CAP) for the exposure studies will be conducted using state-of-the-art high temporal resolution monitoring methods. An important and innovative part of the ECC is the use of the Semi-continuous Elements in Aerosol Sampler (SEAS), combined with high-resolution inductively coupled plama-mass spectroscopy (HR-ICP-MS) analysis, to perform sub-hourly multi-elemental analysis of PM2.5 samples. Many previous CAP studies have not included extensive exposure characterization and thus did not allow evaluation of the contribution of specific PM components to observed health responses. Similarly, source apportionment in the context of CAP studies has been extremely limited, with only few studies using factor analytical techniques to assess the impact of particle sources on toxicological responses. The ECC will incorporate extensive PM characterization and source apportionment in order to determine which PM components, as well as PM emission sources, are associated with toxicological responses.

Expected Results: The GLACIER will provide one of the most comprehensive experiments designed to address the toxicity of components and sources of PM2.5 from several different source types prominent across the Great Lakes region and also, by use of the mobile exposure laboratories, at “real-world” exposure locations. We will provide substantial new information regarding the character and sources of PM2.5 in several settings by use of the novel high-time resolution exposure characterization methods.

CORE: Biostatistics and Data Management

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EPA Grant Number: R834797-01

Project Summary:

Objectives: The objectives of the GLACIER Biostatistics and Data Management Core (BDMC) are to provide guidance for the statistical design and analysis of studies and data management services that allow for the integration of the data into a single platform that facilitates timely analysis for GLACIER investigators and projects. Specific aims for this CORE are (1) to assist GLACIER investigators with statistical and data aspects of their research by providing expertise in the design, conduct and analysis of studies in Projects 1-3; (2) to establish a database for each project on a secure computerized system; and (3) to implement a website to allow data import and export in a secured, controlled environment with a user-friendly interface.

Approach: Aim 1. The core biostatisticians were involved in designing the preliminary analytic plans in the proposals, but as the research progresses the team will adapt to the analytic needs of the projects and will collaborate on new modeling and methodological issues that may arise. This will be accomplished by reviewing data periodically during the conduct of the study to assess distributional and other model assumptions that will inform the development of models and methods. Beyond the standard analytical and design needs, the BDMC will focus on certain methodological challenges in the context of modeling mixtures of multipollutants that are closely related to Projects 1-3, such as (1) the issue of fitting random effects threshold models, (2) the choice of variable selection and use of functional data analytic techniques with high frequency correlated data and multiple pollutants, and (3) identification of exposure windows of vulnerability. Aim 2. Separate Oracle® database will be developed for each study project. Data structures will be flexible to allow for the storage of the study data in multiple ways, specific to each study design. SAS data files, codebooks and study reports will be available on the web, allowing access to the researchers and the analysts. Aim 3. A network-only (internal) web site for the GLACIER team will be created and maintained. Access to privileged information on the web site will be granted using password authentication. Any information that is transferred between the web server and remote sites will be encrypted to ensure security.

Expected Results: The success of the GLACIER BDMC will be the timely completion of analyses owing to the integration of biostatisticians and clinical study professionals in all aspects of the studies – from design of studies and data collection instruments, quality control measures and monitoring during the conduct of the studies, and development of analysis plans with close collaboration with clinical investigators. Thus, the publication of study findings in a timely manner, with application of innovative and rigorous statistical methods, is the ultimate expected result of this Core.